REMARKS

Claims 1, 3, 7, 9-16, and 25 are pending in this application. Claim 25 is rejected under 35 U.S.C. § 102(b) for anticipation by Brown et al. (RE 33,221; hereinafter "Brown"). Claims 1, 3, 7, 9-16, and 25 are rejected under 35 U.S.C. § 103(a) for obviousness over Simkiss et al. (WO 94/02412; hereinafter "Simkiss") alone, and over Simkiss in combination with Brown. Finally, claims 1, 3, 7, 9-16, and 25 are rejected for obviousness-type double patenting over claims 1-14 of U.S. Patent No. 6,214,368 (hereinafter "the '368 patent"), claims 1-2 of U.S. Patent No. 6,132,463 (hereinafter "the '463 patent"), claims 1-21 of U.S. Patent No. 6,027,742 (hereinafter "the '742 patent"), and claims 1-9 of U.S. Patent No. 6,331,312 (hereinafter "the '312 patent"). By this reply, Applicants address each of the Examiner's rejections.

Rejections under 35 U.S.C. § 102(b)

The first ground of rejection is the rejection of claim 25 for lack of novelty over Brown. It is the Examiner's position that Brown discloses a paste that is prepared using the same components as Applicants' paste and that hardens to a "bone like consistency." The Examiner argues that there is no difference between the two pastes and that Appellants have only described the claimed paste differently (i.e., by using the term "PCA" rather than the term "hydroxyapatite" as is used by Brown; Office Action, p. 4). Applicants respectfully traverse this rejection.

The Legal Standard For Anticipation Under 35 U.S.C. § 102(b)

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). *See also EMI Group North*

America, Inc. v. Cypress Semiconductor Corp., 268 F.3d 1342, 1350 (Fed. Cir. 2001) ("A prior art reference anticipates a patent claim if the reference discloses, either expressly or inherently, all of the limitations of the claim."); MPEP § 2131. *Cf. Schering Corp. v. Geneva Pharm., Inc.*, No. 02-1540, 2003 WL 21767852, at *2 (Fed. Cir. Aug. 1, 2003) ("A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention."); *Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1375 (Fed. Cir. 2002) ("A patent is invalid for anticipation when the same device or method, having all of the elements contained in the claim limitations, is described in a single prior art reference.").

"A single reference must describe the claimed invention with *sufficient precision and detail* to establish that the subject matter existed in the prior art." *Verve, LLV v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002) (emphasis added). *See also Crown Operations Int'l, Ltd.*, 289 F.3d at 1357 ("An anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed in the prior art and that such existence would be recognized by persons of ordinary skill in the field of the invention."); MPEP § 2131 ("The identical invention must be shown in as complete detail as is contained in the claim."). "[T]he words of a claim 'are generally given their ordinary and customary meaning.'" *Phillips v. AWH Corporation*, 415 F.3d 1303, 1312 (Fed. Cir. 2005), *citing Vitrionics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir.1996).

Claim 25 is Not Anticipated By Brown

Independent claim 25 reads as follows:

25. A method for embedding a prosthetic device, comprising:
introducing a prosthesis at an implant site;
applying a paste to a surface of the prosthesis, the paste comprising an amorphous calcium phosphate, a poorly crystalline apaptitic (PCA) calcium phosphate, and a

physiologically acceptable fluid in an amount sufficient to provide a paste of formable or injectable consistency, wherein the paste is injectable or formable for a time greater than about 10 minutes at about 25°C and hardens within about 10 to 60 minutes at about 37°C, whereby the paste is converted at the implant site to a hardened PCA calcium phosphate product in an endothermic process; and

allowing the hardened PCA calcium phosphate to be resorbed and replaced thereby with bone. (Emphasis added.)

Claim 25 requires applying a paste prepared by mixing an amorphous calcium phosphate, a poorly crystalline apaptitic (PCA) calcium phosphate, and a physiologically acceptable fluid to a surface of a prosthesis. The paste hardens to form a PCA calcium phosphate, not an hydroxyapatite.

Brown, in contrast, discloses dental remineralizers and dental cements prepared by reacting tetracalcium phosphate ("TTCP") with a specially selected second calcium phosphate to form hydroxyapatite. According to Brown,

> the present invention relates to compositions for remineralizing caries lesions. The invention concerns a combination of $Ca_4(PO_4)_2O$ (tetracalcium phosphate) and at least one other sparingly soluble calcium phosphate solid in equilibrium or quasi equilibrium with a dilute aqueous solution such that both calcium phosphates are present in excess and form a slurry. The other calcium phosphates that may be used are $CaHPO_4.2H_2O$ (dicalcium phosphate dihydrate or brushite), $CaHPO_4$ (monetite), $Ca_8H_2(PO_4)_6.5H_2O$ (octacalcium phosphate), α-$Ca_3(PO_4)_2$, β-$Ca_3(PO_4)_2$ (tricalcium phosphates), and tricalcium phosphates modified by the addition of protons or up to approximately 10% magnesium by weight (whitlockite). (Brown, col. 3, lines 36-49.)

Brown further states:

> All combinations of these calcium phosphates can precipitate *hydroxyapatite* according to the present invention. To do so, however, *the two calcium phosphates must be in near equilibrium with the same saturated solution*; furthermore, the saturated solution [must] be supersaturated with respect to hydroxyapatite. If these conditions are met, the above combinations of calcium phosphates will react to form *hydroxyapatite*. *Since the two calcium phosphates are present in excess*, the solution will remain supersaturated with respect to hydroxyapatite and will continue to precipitate this basic constituent of tooth and bone. (Col. 3, lines 49-60; emphasis added.)

As is clear from the recited passages, Brown teaches the combination of calcium phosphate components that are selected to form a cement that sets to form stoichiometric (i.e., crystalline) hydroxyapatite (HA), not a PCA calcium phosphate, as is recited in independent claim 25 (see Brown, col. 3, lines 36-60 and col. 6, line 51 to col. 7, line 3). It is well understood in the calcium phosphate arts that HA and PCA calcium phosphate are different compositions and not simply the same composition described using different terms (see, e.g., Pleshko et al., Biophys. J. 60:786-793, 1991; a copy of which is provided as Exhibit C). Thus, on this basis alone, Applicants respectfully submit that the rejection of claim 25 under 35 U.S.C. § 102(b) over Brown should be withdrawn.

Brown Fails to Teach a Paste Comprising an Amorphous Calcium Phosphate (ACP), a Poorly Crystalline Apaptitic (PCA) Calcium Phosphate, and a Physiologically Acceptable Fluid that Sets to Form a PCA Calcium Phosphate as Recited in Independent Claim 25

In the August 19, 2005, Office Action, the Examiner asserted that Brown's teaching of "a mixture of two sparingly soluble calcium phosphates and a dilute aqueous solution" anticipated the claimed invention (Office Action, p. 3). The Examiner provided the following explanation in support of this rejection:

> the instant specification on page 7 discloses that a PCA calcium phosphate has **substantially** the same X-ray diffraction spectrum as bone. The examiner points out that Brown on column 9, lines 5-6 discloses the paste hardens to a "bone-like consistency". Therefore, since Brown teaches the same components that form the paste and harden within the same time, applicant's claims read on Brown's disclosure, it is the examiner's position that Brown's bone like implant reads on the instant PCA product, the only difference is in that applicant uses the term "PCA" and the prior art's use of "hydroxyapatite". (August 19, 2005 Office Action, page 4.)

Applicants fail to see how the evidence provided by the Examiner is sufficient to show that Brown describes the claimed invention "with sufficient precision and detail to establish that the subject matter existed in the prior art." (*Verve, LLV, supra.*) Brown nowhere discloses the

use of a paste prepared by mixing an ACP and a PCA with a physiological acceptable fluid, much less that the paste hardens to form a PCA calcium phosphate. The Examiner merely relies on a vague description of the physical properties of the Brown HA composition as having a "bone-like consistency." Applicants submit that this is simply insufficient to demonstrate that Brown discloses the invention of independent claim 25 with the specificity required to support an anticipation rejection under 35 U.S.C. § 102(b).

As is discussed above, Brown clearly discloses the preparation of a paste by mixing tetracalcium phosphate with a second calcium phosphate (Brown, col. 3, lines 36-49). This is further emphasized in Brown's working examples, all of which disclose the preparation of compositions containing tetracalcium phosphate. Brown clearly states that the Brown paste hardens to form a hydroxyapatite (see col. 3, lines 49-57). Brown does not teach or suggest that the paste hardens to form a PCA calcium phosphate, as is required by independent claim 25. To support the rejection, the Examiner merely relies on Brown's vague description of the hardened paste as having a "bone-like consistency" and argues that "the only difference is in that applicant uses the term 'PCA' and the prior art's use of 'hydroxyapatite." The Examiner, though, has utterly ignored the distinction that the art has given to these terms (as is discussed above). When examining a claim, the Examiner must give the words of the claim their "plain meaning," unless they are defined in the specification (see M.P.E.P. § 2111.01(I)). M.P.E.P. § 2111.01 (II) clarifies that the "plain meaning" refers to the "ordinary and customary meaning" given to the word by a person of ordinary skill in the art in question at the time of the invention (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) (*en banc*)). In this case, Applicants' specification has not defined the terms "poorly crystalline apatitic (PCA) calcium phosphate" or "hydroxyapatite" contrary to their ordinary and customary meanings. In

fact, Applicants' specification clearly distinguishes between PCA calcium phosphate and hydroxyapatite by teaching:

> The poorly crystalline apatitic calcium phosphate of bone is distinguished from the more crystalline hydroxyapatites and non-stoichiometric hydroxyapatites by its distinctive x-ray diffraction pattern as shown in FIG. 1. Unlike the ideal stoichiometric crystalline hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, with atomic Ca/P ratio of 1.67, the composition of bone mineral is significantly different and may be represented by the following formulae,
>
> $$Ca_{8.3}(PO_4)_{4.3}(HPO_4,CO_3)_{1.7}(OH,CO_3)_{0.3}.$$
>
> Bone mineral non-stoichiometry is primarily due to the presence of divalent ions, such as CO_3^{2-} and HPO_4^{2-}, which are substituted for the trivalent PO_4^{3-} ions. Substitution by HPO_4^{2-} and CO_3^{2-} ions produces a change of the Ca/P ratio, resulting in Ca/P ratio which may vary between 1.50 to 1.70, depending on the age and bony site. (Specification, p. 1, line 21, through page 2, line 5.)

The Examiner overlooks this distinction entirely, arguing only that Applicants have chosen the terms without distinguishing them. This Applicants need not do because the terms have distinct meanings in the art and Applicants have not used the terms contrary to their known meanings.

As further evidence, Applicants provide the enclosed Declaration of Dr. Michael Strunk, which confirms several important differences between the PCA calcium phosphate recited in independent claim 25 and the hydroxyapatite of Brown. The Declaration states that Applicants' PCA calcium phosphate is a carbonate hydroxyapatite, the chemical structure of which is $Ca_a(PO_4)_b(HPO_4,CO_3)_c(OH,CO_3)_d$, where a, b, c, and d are *non-stoichiometric* and carbonate is part of the chemical composition of the final product (see ¶ 4, Declaration of Dr. Michael Strunk and the FTIR spectra shown in Exhibit B enclosed with the Strunk Declaration; and Example 2, page 32, line 19, through page 33, line 13, of the specification). The substitution of carbonate ions for phosphate ions during the formation and hardening of the PCA calcium phosphate produces gaps in the crystal lattice. It is these gaps which reduce crystalline formation and that

impart the "poorly crystalline" characteristic to the resulting apatitic calcium phosphate material of independent claim 25. These gaps constitute one distinction between Applicants' PCA calcium phosphate and the hydroxyapatite of Brown, which lacks these gaps. Because Applicants' PCA calcium phosphate is poorly crystalline, it remains soluble and is easily resorbed and replaced by bone once hardened in the body; a further characteristic that is recited in independent claim 25.

As a further distinction, Brown teaches that the two calcium phosphate constituents are provided in near equilibrium during the formation of the hydroxyapatite (see col. 3, lines 49-55). Thus, the hydroxyapatite formed by the Brown method is necessarily a *stoichiometric hydroxyapatite*, and not a PCA calcium phosphate, as is recited in independent claim 25; this is true whether Brown prepares the hydroxyapatite using calcium phosphates in crystalline, cryptocrystalline, or amorphous form (see col. 10, lines 11-31). Thus, Brown simply fails to teach or suggest the preparation of a hardened calcium phosphate having a non-ordered crystal lattice, which is an inherent property of the PCA calcium phosphate of independent claim 25. Furthermore, unlike PCA calcium phosphate, stoichiometric hydroxyapatite is sparingly soluble, and thus, not easily resorbed by the body and replaced by bone. Therefore, for all of the reasons discussed above, the hydroxyapatite composition disclosed by Brown, while bone-like, is not the same as Applicants' PCA calcium phosphate.

Because Brown fails to teach or suggest all of the elements of present claim 25, Applicants respectfully request that the rejection of claim 25 under 35 U.S.C. § 102(b) over Brown be withdrawn.

Rejections under 35 U.S.C. § 103(a)

The second ground of rejection is the rejection of pending claims 1, 3, 7, 9-16, and 25 for obviousness over Simkiss. As the Examiner states, Simkiss discloses a precursor material that can be applied to a site where bone growth is required and that hardens to form bone *in vivo* (Office Action, p. 4). The Examiner admits that Simkiss "exemplifies a material wherein the material is hardened after 'many hours,'" but further asserts that Simkiss teaches how to modify the material to produce both fast-setting and slow-setting materials (Office Action, pp. 4-5). The Examiner concludes by stating that although the recited setting time is not disclosed by Simkiss, it would be obvious to one of ordinary skill in the art at the time the invention was made to formulate a fast-setting material. Finally, the Examiner asserts that there is no difference between Applicants' recited "PCA" calcium phosphate and Simkiss' "hydroxyapatite" in view of the similarities between the X-ray diffraction spectra of the two compositions; the Examiner invites comparison of Fig. 2 of Appellants' application to Fig. 1 of Simkiss (Office Action, p. 6). Applicants respectfully traverse this rejection.

The Legal Standard for Obviousness Under 35 U.S.C. § 103(a)

A claimed invention is unpatentable if the differences between it and the prior art are such that the claimed subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *See* 35 U.S.C. § 103(a) (2003). Correspondingly, the conclusion regarding obviousness of a claimed invention is based upon the following four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations of nonobviousness

(*e.g.*, commercial success, long-felt but unsolved needs, failure of others). *See McNeil-PPC, Inc. v. L. Perrigo Co.*, No. 02-1516, 2003 U.S. App. LEXIS 15442, at *14, -- F.3d -- (Fed. Cir. Aug. 1, 2003) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)); *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124 (Fed. Cir. 2000) (same); *Ex Parte Crinion*, No. 2001-0210, 2002 WL 31257831, at *2 (Bd. Pat. App. & Interf. 2001) (same); MPEP § 2141.

Three criteria are required to establish a *prima facie* case of obviousness:

First, "[t]here must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor." *Id.* at 1376. *See also Brown & Williamson Tobacco Corp.*, 229 F.3d at 1124-25 ("[A] showing of a suggestion, teaching or motivation to combine the prior art references is an essential evidentiary component of an obviousness holding. This evidence may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved." (internal citations omitted)); *Ex Parte Metcalf*, 67 U.S.P.Q.2d 1633, 1635 (Bd. Pat. App. & Interf. 2003) ("Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination."); MPEP § 2143.01. The "[d]etermination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Crown Operations Int'l, Ltd.*, 289 F.3d at 1376.

The requisite teaching, suggestion, or motivation must be "clear and particular;" broad conclusory statements will not suffice. *See Brown & Williamson Tobacco Corp.*, 229 F.3d at

1125; *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000) ("Whether the Board relies upon an express or implicit showing, it must provide particular findings related thereto. Broad conclusory statements are not 'evidence.'" (internal citations omitted)). A statement that modification of the prior art would have been "within the capabilities of one skilled in the art" will not, therefore, suffice to establish a *prima facie* case of obviousness. *See In re Kotzab*, 217 F.3d at 1371 (reversing the Board's finding of obviousness, stating that "there was no finding as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of [the inventor's] invention to make the combination in the manner claimed."); *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) ("Rarely, however, will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment."); MPEP § 2143.01. As the Board itself stated in overturning an examiner's obviousness rejections based on a proposed modification of the prior art:

> In this case, however, the only suggestion for the examiner's combination of the isolated teachings of the applied references improperly stems from appellant's disclosure and not from the applied prior art. *At best, the examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness. That which is within the capabilities of one skilled in the art is not synonymous with obviousness.* That one can reconstruct and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless that logic and reasoning also supplies sufficient impetus to have led one of ordinary skill in the art to combine the teachings of the references to make the claimed invention. *Ex Parte Levengood*, 28 U.S.P.Q.2d 1300, 1301-02 (Bd. Pat. App. & Interf. 1993) (internal citations omitted; emphasis added)).

Second, there must be a reasonable expectation of success that modification or combination of the prior art will achieve the claimed invention. *See Brown & Williamson Tobacco Co.*, 229 F.3d at 1125 ("[T]he ultimate determination of obviousness does not require

absolute predictability of success. All that is required is a reasonable expectation of success." (internal references omitted)); MPEP § 2143.02. There can be neither a motivation to modify or combine prior art nor a reasonable expectation of success when doing so would alter the principles of operation underlying that art. *See* MPEP § 2143.01.

Third, the prior art reference(s) must teach or suggest all the claim limitations. *See* MPEP § 2143.03.

Claims 1, 3, 7, 9-16, and 25 are Not Obvious Over Simkiss Alone

The text of independent claim 25 is discussed above. Independent claim 1 reads as follows:

> 1. A method for treating a bone defect, comprising:
> providing a strongly resorbable, synthetic poorly crystalline apatitic (PCA) calcium phosphate that is injectable or formable for a time greater than about 10 minutes at about 25°C and that hardens within about 10 to 60 minutes at about 37°C, the poorly crystalline apatitic calcium phosphate having a calcium to phosphate (Ca/P) ratio in the range of about 1.2 to 1.68 and further having the X-ray diffraction pattern of naturally occurring bone, and
> implanting the poorly crystalline apatitic calcium phosphate at an implant site requiring bone growth, whereby the implanted poorly crystalline apatitic calcium phosphate is resorbed with a resorption rate characterized in that, when placed in a rat intramuscular site, at least 1 g of the poorly crystalline apatitic calcium phosphate is at least 80% resorbed within one year, and bone is formed at the implant site. (Emphasis added.)

Claim 1, and claims dependent therefrom, require providing a strongly resorbable, synthetic poorly crystalline apatitic (PCA) calcium phosphate that is injectable or formable for a time greater than about 10 minutes at about 25°C and that hardens within about 10 to 60 minutes at about 37°C. The PCA calcium phosphate has a calcium to phosphate (Ca/P) ratio in the range of about 1.2 to 1.68, an X-ray diffraction pattern of naturally occurring bone, and, once

implanted, at least 1 gram of the PCA calcium phosphate is at least 80% resorbed within one year.

Simkiss describes preparing crystalline hydroxyapatite. Simkiss states:

> At its simplest, a precursor material is an amorphous composition which contains calcium and phosphate ions as primary constituents together with inhibitor components (notably magnesium and/or pyrophosphate ions) which inhibit its transformation to a crystalline form (generally based on hydroxyapatite). (Simkiss, page 2, line 33, through page 3, line 2).

Simkiss further discloses that leaching of the inhibitor components promotes the transformation of the amorphous calcium phosphate composition into crystalline hydroxyapatite (Simkiss, p. 3, lines 2-6). Simkiss further teaches that the conversion of "amorphous material into bone material is slow, e.g., taking days, so that it is likely to integrate into normal healing processes" (Simkiss, p. 3, lines 17-20).

Simkiss Alone Fails to Teach or Make Obvious a Poorly Crystalline Apaptitic (PCA) Calcium Phosphate as Recited in Independent Claims 1 and 25

The Examiner explains the obviousness rejection of the pending claims as follows:

> Simkiss et al teach an amorphous calcium phosphate that hardens to form bone in vivo...The precursor material is applied to the site where bone growth is required...Simkiss teaches the precursor material contains the inhibitors in low levels, which inhibit the crystallization of the material, and when the implant is in vivo, the inhibitors are leached away by body fluid, thus causing the precursor material to undergo transformation into crystalline hydroxyapatite...Simkiss teaches transformation time can be controlled by the choice of inhibitor and the choice of inhibitor concentration and/or solubility.
>
> ****
>
> Simkiss does not teach the recited setting time.
>
> ****
>
> However, it is deemed obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Simkiss and formulate a fast-setting precursor material.

The Examiner further asserts:

> the instant specification...discloses that an amorphous calcium phosphate is converted into the poorly crystalline apatitic calcium phosphate having the X-ray diffraction spectrum similar to that of bone wherein the spectrum is generally characterized by only two broad peaks in the region of 20-35 degrees with one centered at 26 degrees and the other centered at 32 degrees. This is the same spectrum taught by Simkiss (see Figure 1). Thus, the examiner does not see a patentable distinction between the instant PCA product and that of Simkiss's product except in the applicant's use of the term "PCA" and the prior art's use of "hydroxyapatite". (Office Action dated August 19, 2005, pp. 7-8.)

As is discussed above, Applicants' invention features the use of a PCA calcium phosphate, as is recited in independent claims 1 and 25. In contrast, Simkiss discloses the preparation and use of stoichiometric crystalline hydroxyapatite (see, e.g., p. 2, line 33, through p. 3, line 6, of Simkiss). The Examiner states that there is no

> patentable distinction between the instant PCA product and that of Simkiss's product except in the applicant's use of the term "PCA" and the prior art's use of "hydroxyapatite". If applicant asserts there is a distinction, the examiner suggests providing evidence to demonstrate this. (Office Action, pp. 7-8.)

Applicants again direct the Examiner to the Declaration of Dr. Michael Strunk, which points out that there are distinct differences between the PCA calcium phosphate of present claims 1, 3, 7, 9-16, and 25 and the hydroxyapatite of Simkiss.

Dr. Strunk states that Applicants' PCA calcium phosphate is a *non-stoichiometric* calcium phosphate formed by incorporating carbonate ions in place of phosphate ions in the crystal lattice of the hardened calcium phosphate product, which increases the solubility of the final product and, by extension, its resorbability (see ¶ 4 of the Declaration). In contrast, Simkiss teaches the preparation of stoichiometric hydroxyapatite according to a two-step process (discussed in further detail below). Dr. Strunk also states that Applicants' PCA calcium phosphate is formed rapidly and directly by nucleation and growth at low temperatures (within minutes from a malleable paste) to a hardened solid, as is recited in present claims 1, 3, 7, 9-16, and 25. In contrast, Simkiss discloses a pre-product that precipitates from solution over a long

period of time (hours), and requires the removal of inhibitor ions (i.e., Mg^{2+}) by leaching from the composition for hardening to occur. At hardening, the Simkiss composition converts to ordered, stoichiometric hydroxyapatite as a consequence of the resulting chemical reaction; it does not form a non-stoichiometric PCA calcium phosphate, as is recited in present claims 1, 3, 7, 9-16, and 25 (¶ 6 of the Declaration). Thus, the PCA calcium phosphate recited in independent claims 1 and 25 is distinct from that of Simkiss for all of these reasons. Thus, in view of these differences, Simkiss fails to teach or suggest the PCA calcium phosphate recited in independent claims 1 and 25, and claims dependent therefrom.

In addition, Applicants point out that present claims 1, 3, 7, and 9-16 are limited to a *synthetic* PCA calcium phosphate. Simkiss discloses the preparation of two calcium phosphate materials: a synthetic HA and a calcium phosphate prepared using *naturally occurring* material derived from *C. maenas* (see page 3, lines 31-34; page 4, lines 17-19). Simkiss only characterizes by XRD the naturally occurring material (see trace A of Fig. 1, which provides the XRD pattern of naturally occurring material that contains inhibitor ions; and trace B of Fig. 1, which provides the XRD pattern of the same naturally occurring material that has been washed to remove ions that prevent hardening of the material (i.e., "inhibitor ions"), and dried to allow hardening). Although Simkiss discloses the preparation of synthetic HA, Simkiss fails to chemically characterize the synthetic HA by providing an XRD pattern of this material. The Examiner, though, in making the rejection of present claims 1, 3, 7, and 9-16, relies on the XRD pattern shown in Fig. 1 of Simkiss, stating that the XRD pattern that characterizes Applicants' PCA calcium phosphate

> is the same spectrum taught by Simkiss (see Figure 1). Thus, the examiner does not see a patentable distinction between the instant PCA product and that of Simkiss's product except in the applicant's use of the term "PCA" and the prior art's use of "hydroxyapatite". (Office Action, pp. 7-8.)

Fig. 1 of Simkiss provides only the XRD pattern of the naturally occurring calcium phosphate disclosed by Simkiss and not the actual synthetic HA prepared by Simkiss. Thus, the Examiner's comparison of the XRD pattern of Fig. 1 of Simkiss and Applicants' XRD pattern for PCA calcium phosphate shown in, e.g., Fig. 3(c), is misguided, as these two spectra are not the same. Thus, for this reason, Fig. 1 of Simkiss does not support the Examiner's rejection of independent claims 1 and 25, and claims dependent therefrom, under 35 U.S.C. § 103(a) over Simkiss.

Moreover, even if the calcium phosphate material characterized in Fig. 1 of Simkiss was deemed to be synthetic material, which it is not, this alone would still be insufficient to demonstrate that the material disclosed and characterized by Simkiss is equivalent to Applicants' PCA calcium phosphate. The X-ray diffraction (XRD) pattern of Applicants' PCA calcium phosphate is clearly distinct from that shown in Fig. 1 of Simkiss based on the presence of peaks at ~28° 2 x theta (see Exhibit B, provided herewith, and Fig. 3c of the present application). The XRD pattern disclosed in Fig. 1 of Simkiss shows that Simkiss' hydroxyapatite lacks any distinct peaks at ~28° 2 x theta. Thus, because the material characterized in Fig. 1 of Simkiss is naturally occurring (and notwithstanding the other differences between this material and Applicants' PCA calcium phosphate discussed above), Applicants submit that the Examiner cannot rely on Fig. 1 of Simkiss as teaching or suggesting Applicants' synthetic PCA calcium phosphate.

Thus, for all of these reasons, Simkiss fails to teach or suggest the PCA calcium phosphate recited in independent claims 1 and 25, and claims dependent therefrom. Because Simkiss fails to teach or suggest all of the elements of present claims 1, 3, 7, 9-16, and 25, Applicants respectfully request that the rejection of claims 1, 3, 7, 9-16, and 25 under 35 U.S.C. § 103(a) for obviousness over Simkiss be withdrawn.

Simkiss in Combination with Brown Fails to Teach or Suggest a Poorly Crystalline Apaptitic (PCA) Calcium Phosphate as Recited in Independent Claims 1 and 25

The third ground of rejection is the rejection of pending claims 1, 3, 7, 9-16, and 25 for obviousness over Simkiss in view of Brown. The Examiner reiterates the description of Simkiss, as is discussed above under the second ground of rejection, and states that Brown is relied upon "for its specific teaching of manipulating setting times of the paste" (Office Action, p . 11). Again the Examiner asserts that Applicants' use of the term "PCA" does not distinguish the calcium phosphate recited in present claims 1, 3, 7, 9-16, and 25 from the "hydroxyapatite" of Simkiss and Brown. The Examiner supports the rejection by arguing that Applicants "define[] PCA as having the X-ray diffraction spectrum similar to that of bone wherein the spectrum is [the same as that]...taught by Simkiss (see Figure 1)" (Office Action, pp. 10-11). The Examiner further states that "the only teaching lacking in Simkiss is the instant setting time. Therefore, the examiner relies on Brown for its specific teaching of manipulating setting times of the paste. The combination of Simkiss in view of Brown as a whole suggests the instant invention" (Office Action, p. 11). Applicants respectfully traverse this rejection.

As is discussed above, neither Simkiss nor Brown disclose the preparation of a PCA calcium phosphate, as is recited in present claims 1, 3, 7, 9-16, and 25; Simkiss and Brown only disclose the preparation of a crystalline, stoichiometric hydroxyapatite material. Moreover, as evidenced by the Declaration of Dr. Michael Strunk, the X-ray diffraction spectrum of Applicants' PCA calcium phosphate is different from the X-ray spectrum shown in Figure 1 of Simkiss based on the presence of a minor peak at ~28° 2 x theta (see Figure 3b of Applicants' specification). Finally, Applicants again point out that Simkiss only characterizes naturally-

derived material (Simkiss, p. 4, lines 17-28); Simkiss fails to disclose the X-ray diffraction pattern of the synthetic hydroxyapatite material.

For all of the reasons discussed above, Simkiss and Brown, either singly or in combination, fail to teach or suggest all of the limitations of present independent claims 1 and 25, and claims dependent therefrom. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the rejection of claims 1, 3, 7, 9-16, and 25 under 35 U.S.C. § 103(a) for obviousness over Simkiss in combination with Brown be withdrawn.

Obviousness-type Double Patenting Rejection

The Examiner rejects claims 1, 3, 7, 9-16, and 25 for obviousness-type double patenting over claims 1-14 of the '368 patent, claims 1-2 of '463 patent, claims 1-21 of the '742 patent, and claims 1-9 of the '312 patent. Applicants acknowledge the Examiner's withdrawal of the rejection of claims 1, 3, 7, 9-16, and 25 over claims 13-27 of U.S. Patent No. 6,287,341. In the event the pending claims are found to be otherwise allowable, Applicants will consider the appropriateness of filing a terminal disclaimer to overcome this rejection.

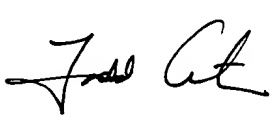
CONCLUSION

In view of the above remarks, Applicants respectfully submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for five months, to and including September 27, 2006, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully Submitted,



TODD ARMSTRONG, Ph.D.
Reg. No. 54,590

Date: 27 September 2006

For Paul T. Clark
Reg. No. 30,162

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: (617) 428-7002
Facsimile: (617) 428-7045